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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/809,144	03/25/2004	Robert Costa	03-284-E	7397

20306 7590 06/27/2007

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EXAMINER	
HALVORSON, MARK	
ART UNIT	**PAPER NUMBER**
1642	

MAIL DATE	DELIVERY MODE
06/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/809,144	COSTA ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-49* is/are pending in the application.

4a) Of the above claim(s) *4-7 and 12-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10 and 12-49 are pending.

Claims 4-7 and 12-49 have been withdrawn.

Claims 1-3 and 8-10 are under currently under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

35 USC § 102(b) rejections withdrawn

The rejection of claims 1-3, and 8, under 35 U.S.C. 102(b) as being anticipated by Sherr et al is withdrawn in view of Applicants arguments.

35 USC § 103(a) rejections maintained

The rejection of claims 1, 9-10 under 35 U.S.C. 103(a) as being unpatentable over Sherr et al in view of Laes et al is withdrawn in view of Applicants arguments

NEW REJECTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting proliferation of a tumor cell comprising the step of inhibiting FoxM1B activity in the tumor cell by contacting the cell with a p19ARF protein fragment *in vitro*, does not reasonably provide enablement for a method of inhibiting proliferation of a tumor cell comprising the step of inhibiting FoxM1B activity in the tumor cell by contacting the cell with a p19ARF protein fragment

in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make o ruse the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to a method of inhibiting proliferation of a tumor cell comprising the step of inhibiting FoxM1B activity in the tumor cell by contacting the cell with a p19ARF protein fragment. The claims are interpreted to read on a method for inhibiting proliferation of a tumor cell *in vivo*.

The specification discloses that the p19 associates with endogenous FoxM1B proteins in liver cells following treatment with DEN/PB. (Example 15). The specification further discloses that the peptide of SEQ ID NO:10 comprising a p19ARF protein fragment can associates with FoxM1B and inhibit the transcriptional activity of FoxM1B. (Example 18). In addition, the peptide of SEQ ID NO:10 inhibited the FoxM1B colony formation of a human osteoblastoma cell line. (Example 20). There is no disclosure in the specification on the inhibition of tumor cell proliferation *invivo* by the p19ARF protein fragment of SEQ ID :10.

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification teaches a method for inhibiting tumor cell lines *in vitro* while the claims encompasses a method for inhibiting tumor cell lines *in vivo*

Those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon

such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in- vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Furthermore, Zips et al state that "It is obvious that cells in culture represent an artifical and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and, thereby drug accces to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugss that does not exist *in vitro*. **Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential**." (In Vivo, 2005, 19:1-7)

It is well known in the art that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the p19ARF protein fragment of SEQ ID NO:10 could function as claimed, that is could be used to inhibit the proliferation of a tumor cell *in vivo* , based only on the finding that the p19ARF protein fragment of SEQ ID NO:10 inhibit the transcriptional activity of FoxM1B in a cell line *in vitro* and inhibited the FoxM1B colony formation of a human osteoblastoma cell line *in vitro*. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess

many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2).

In addition, anti-tumor therapeutic formulations, as claimed, must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition, variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the p19ARF protein fragment of SEQ ID NO:10 could function as claimed, that is could be used to inhibit the proliferation of a tumor cell *in vivo* can be used with a reasonable expectation of success.

In particular, the art also teaches general problems with the administration of peptide and protein drugs, namely short half-life in vivo, necessitating multiple administrations (Johnson and Tracey, 'Peptide and Protein Drug Delivery', In: Encyclopedia of Controlled Drug Delivery, Vol. 2, 1999, pages 816-833). The art teaches that major stability, release and manufacturing challenges" (page 816, second column, lines 1-5) must be met in order to overcome the technical difficulties associated

with the delivery of peptides in vivo. The specification does not specifically teach a method for targeting the small peptide for the delivery to the appropriate site or teach the efficacious uptake to result in the inhibition of tumor-growth in a patient. Thus, one could not predict that the half-life of the claimed peptide is sufficient to function as claimed, that its stability is sufficient, how many administrations are required in order to function as claimed, or even whether or not the peptide is able to function as claimed

Given the lack of predictability of the in vivo administration of a peptide drug to inhibit the proliferation of a tumor cell, the lack of working examples and the lack of specific guidance in the specification one could not predict whether the p19ARF protein fragment of SEQ ID NO:10 could function as claimed, that is could be used to inhibit the proliferation of a tumor cell in vivo with a reasonable expectation of success.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be reasonably be predicted that the p19ARF protein fragment of SEQ ID NO:10 could function as claimed, that is could be used to inhibit the proliferation of a tumor cell *in vivo*. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims, the lack of guidance and support in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Summary

Claims 1-3 and 8-10 stand rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at (571) 272-0898. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the

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